Further, a Hp-Hb complex, or a part thereof or a mimic thereof being operably linked to a substance, wherein the Hp-Hb complex is capable of binding said CD163 molecule is also within the scope of the invention.

In the present context the word medicament is used in its normal meaning as a composition to be administered to an individual for prophylactic, therapeutic and/or diagnostic purposes.

Figures

Fig. 1: is an illustration of the steps involved in the Hp-Hb/CD163 binding.

Fig. 2: shows examples of 2a) a haptoglobin dimer, 2b) haptoglobin multimers, 2c) Hp-Hb complexes, and 2d) a SDS-PAGE gel of mono- and multimers of haptoglobin.

Fig. 3: shows a CD163 molecule.

Fig. 4: shows 9 different haptoglobin sequences

Fig. 5: shows 4 different CD163 sequences

Fig. 6: Binding of Hp-Hb to CD163. **a,** Illustration of the subunit organisation and disulfide bridging of the various Hp and Hp-Hb complexes. The inset shows non-reducing SDS-PAGE of the Hp(1-1) dimer and Hp(2-2) multimers. **b**, Surface plasmon resonance analysis of the binding of Hp-Hb to CD163. The measurements were carried out at Hb concentrations ranging from zero to 100 µg/ml in the absence of Hp (left panel), or in the presence of 50 µg/ml of Hp(1-1) (middle panel), and 50 µg/ml Hp(2-2) (right panel). No binding was observed with either Hb or Hp alone, and saturation of the binding was obtained at 50 µg/ml Hb for both Hp phenotypes. **c**, Inhibition of CD163-binding of ^{125}I-labelled Hp(1-1)-Hb (left panels) and Hp(2-2)-Hb (right panels) by polyclonal anti-CD163 IgG, non-immune rabbit IgG, EDTA (5 mM) and by various concentrations of unlabelled Hp(1-1)-Hb and Hp(2-2)-Hb complexes. CD163 was immobilised in microtiter plate wells.

Fig. 7: CD163-mediated endocytosis of ^{125}I-Hp-Hb. **a**, Cell-association and degradation of ^{125}I-Hp(2-2)-Hb in mock-transfected (left panel) and CD163 cDNA-transfected CHO cells (middle panel). Addition of the lysosomal inhibitors chloroquine and leupeptin (both 100 µM) inhibited degradation leading to cellular accumulation of radioactivity (right panel). **b,** Inhibition of ^{125}I-Hp-Hb uptake in CD163 cDNA-transfected CHO

cells (left panel) and in CD163-expressing histiocytic lymphoma-derived SU-DHL-1 cells (right panel). Both cell types displayed a saturable uptake inhibited by anti-CD163 polyclonal IgG. The insets in a and b show anti-CD163 immunoblotting of the cells.

Fig. 8: Determination of the concentration of sCD163 in the blood of a human donor.

Fig. 9: Fluorescence studied in confocal microscope (example 6).

Fig. 10: Sensogram of the destiny of HbSR and HbSR SRCR domain 1-6.

Fig.11: Selection of Fab antibody phage to Hp-Hb complexes and CD163. The output over input ratio, indicative of selection of clones, is depicted in panels *A* and *C* for the selections on coated Hp-Hb complexes and CD163, respectively. In the panels *B* and *D*, two representative phage ELISAs are shown in which 10 random clones from the third round of selection have been tested. Clones 3, 9 and 10 in panel B represent the Fab1 clone isolated from the Hp-Hb complex-selections and clones 8 and 9 in panel D represent the Fab18 clone isolated from the CD163 selections. In total, 50 clones from each round were screened.

Fig. 12a: Binding of anti-Hp-Hb Fab1-phage to Hp-Hb complexes, Hp and Hb. The binding to Hp-Hb complexes is represented by the circles, to Hp by the squares, to Hb by the diamonds and to BSA by the triangles. The experiment was performed in duplicate. An irrelevant Fab-phage did not show binding to any of the tested antigens under these conditions (not shown).

Fig.12b: Binding of Fab1 to Hp-Hb complexes, Hp and Hb immobilized on a BIAcore sensorchip. Binding of Fab1 to Hb is depicted in panel *A*, to Hp in panel *B* and to Hp-Hb complexes in panel *C*. In each case a concentration range of 0 to 200 nM Fab1 was used.

Fig.13: Fab inhibition of ^{125}I-Hp-Hb (2:2) complex-binding to coated CD163. Curves represent the effects of increasing concentrations of anti-Hp-Hb Fab1 (diamonds), anti-CD163 Fab18 (squares) and irrelevant FabA8 (triangles) on binding of a trace amount of ^{125}I-Hp-Hb complexes to CD163.

Detailed description of the invention

In a first aspect the present invention relates to a Hp-Hb complex or a functional equivalent thereof being operably linked to a substance, said complex and/or functional equivalent thereof being capable of binding to a CD163 receptor and/or a CD163 variant. A functional

equivalent of a Hp-Hb complex is to be understood as any part (or fragment) or any mimic capable of binding to a CD163 receptor.

"Functional equivalency" as used in the present invention is according to one preferred embodiment established by means of reference to the corresponding functionality of a predetermined Hp-Hb fragment.

In the present context the term "Hp-Hb complex" means a complex of at least one haptoglobin chain and at least one haemoglobin chain called a monomeric Hp-Hb complex. Preferably the complex comprises at least one haptoglobin chain and at least one dimeric form of haemoglobin chains. In a further preferred embodiment the complex comprises a multimeric form of haptoglobin chains such as a dimeric form, each haptoglobin chain binding at least one haemoglobin chain, preferably a dimer of haemoglobin chains.

The fragment thereof should be understood to be any part of the Hp-Hb complex capable of binding to the CD163 receptor or to a variant thereof and through said binding activate uptake of the fragment and/or the substance into the CD163 presenting cell.

The mimic thereof should be understood to be any modification of the Hp-Hb complex (in the present context also called a variant of the complex) or any other molecule capable of binding to the CD163 receptor or to a variant thereof and through said binding activating uptake of the fragment and/or the substance into the CD163 presenting cell. Mimics may be peptides, peptide derivatives, antibodies, as well as non-peptide compounds, such as small organic compounds, sugars and fats.

In a preferred embodiment mimics may be antibodies capable of binding to the CD163 receptor, for example in order to elicit uptake of a substance linked to the antibody.

Fragments and/or mimics may be identified by combinatorial chemistry using the CD163 receptor, phase display technique or other techniques known to the person skilled in the art.

The Hp-Hb complex fragment or mimic is preferably, capable of binding to a region in the SRCR domains I-IX of the CD163 receptor, such as capable of binding to a region in the SRCR domains I-VIII of the CD163 receptor, capable of binding to a region in the SRCR domains I-VII of the CD163 receptor, capable of binding to a region in the SRCR domains I-VI of the CD163 receptor, capable of binding to a region in the SRCR domains I-V of the CD163 receptor, capable of binding to a region in the SRCR domains I-IV of the CD163 receptor, capable of binding to a region in the SRCR domains I-III of the CD163 receptor, ca-